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Dated 7th May 1999

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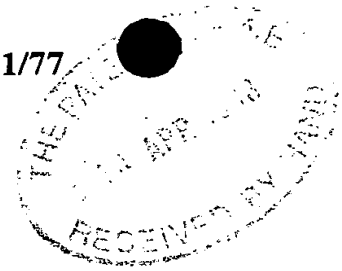

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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Cardiff Road
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1. Your reference — HL55622/000/MRJ

2. Patent application number *(The Patent Office will fill in this part)* — 14 APR 1998 — **9807917.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

STOWIC RESOURCES LIMITED
Ross House
Stow-on-the-Wold
Glos. GL54 1AF

Patents ADP number *(if you know it)*
If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom — 7417360001

4. Title of the invention
METHOD OF MANUFACTURING TRANSDERMAL PATCHES

5. Full name of your agent *(if you have one)* — Haseltine Lake & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Imperial House
15–19 Kingsway
London WC2B 6UD

Patents ADP number *(if you know it)* — 34001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to a grant of patent required in support of this request? *(Answer "Yes" if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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Continuation sheets of this form	
Description	11 —
Claim(s)	CO 15/4/98
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Drawing(s)	1 + 1 —

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to a grant of patent *(Patents Form 7/77*	
Request for preliminary examination and search *Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify*	

11. I/We request the grant of a patent on the basis of this application

Signature

Date
9th April 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

Michael R. Jones

[0117] 9260197

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METHOD OF MANUFACTURING TRANSDERMAL PATCHES

This invention relates to a method of manufacturing transdermal patches, for example the so-called nicotine patches which can be applied to the skin of a person who wishes to receive some nicotine whilst giving up smoking.

One particularly satisfactory form of patch is disclosed in United Kingdom Patent Specification No. 2232892, where it is broadly defined as an occlusive body for the transdermal administration of a physiologically active substance, the body comprising an impermeable backing and a microporous or permeable membrane which define a cavity therebetween, said physiologically active substance being contained within said cavity in liquid form, said microporous or permeable membrane being permeable to and in contact with said physiologically active substance and the liquid material confined between said impermeable backing and said microporous or permeable membrane within said cavity being substantially immobilised by a viscous flowable gel, characterised in that either;

a) said membrane is hydrophilic and the contents of said cavity are hydrophobic; or

b) said membrane is hydrophobic and said cavity contains a hydrophilic wetting agent;

whereby, in use, passage of said physiologically active substance through said microporous membrane is rate-controlling and said physiologically active substance is released from said microporous membrane at a rate that is substantially constant over a period of hours.

Typically the occlusive body in the form of the patch has, in going from one side to the other, several layers which may include: (i) a disposable, removable protective layer, (ii) a layer of adhesive, (iii) the permeable membrane or membranes, (iv) a layer of gel

containing the physiologically active substance (such as nicotine), and (v) the layer of an impermeable backing material.

In practice the first three (or more) layers may be employed as a pre-formed laminate. It is then necessary to apply the active substance (layer (iv)) to the laminate (to the combination of layers (i) to (iii)) and then to secure the active substance in place by providing the backing layer (layer (v)).

Typically when manufacturing a product of this nature, the materials are fed horizontally and a discrete amount of the active substance is deposited at a fixed interval, or station, along the laminate, with the backing material then being brought into position in order to cover the active substance prior to the backing material being secured, for example by sealing, to the laminate in regions around the discrete amounts of active substance. The process is non-continuous and known as 'form, fill, seal' such as is demonstrated by a blister packer. It requires substantial re-tooling if volumetric changes to the reservoir are desired.

Bearing in mind that the active substance is normally present in a gel, it can be appreciated that there are considerable handling problems associated with providing the appropriate amounts of the gel at neatly spaced intervals along the laminate without the gel being exposed to the environment. Moreover, when it is wished to vary the volume of the gel, so as to vary the amount of active substance in the patch, or to vary the skin contact area of the product, (assuming that the concentration of active substance in the gel remains the same), it can be difficult to alter the machine whilst in operation so that the desired effect is achieved.

Equipment already exists for wrapping items such

as so-called telephone cards, which are cards for insertion into a telephone machine to allow the user to use the telephone for the duration of the unused units electromagnetically held in the telephone card. In such equipment a first layer of material is caused to travel vertically downwards close to, and parallel to, a second layer of material. Often one layer is transparent and the other is opaque and contains instructions and other information. The two layers of material are brought together and are sealed to each other by opposing pairs of sealing devices, e.g. heated wheels, which act on the opposing longitudinal edges of the two strips of material being brought together. In addition, an intermittent sealing mechanism acts transversely across the juxtaposed layers already joined at their opposing longitudinal edge regions, so that a pouch results. As the pouch is being formed a telephone card, or the like, is fed into the pouch which still remains open along its upper (fourth) edge. Once the card or other item is correctly located in the pouch, and while both layers continue to move downwardly, the fourth open edge of the pouch is closed, typically by the same horizontal sealing mechanism. In fact, the most efficient way of achieving this is for the upper edge of a lower pouch to be sealed at the same time as the lower edge of the immediately upper pouch is being sealed. Both sealing operations can be carried out simultaneously by the same sealing arrangement.

If desired at about the same time as the sealing is being effected to form the last transverse seal, or immediately downstream thereof or at a much later stage, the pouches can be separated from each other by cutting, or else a line of weakness can be formed in the region between the upper seal of the lower pouch and the lower seal of the upper pouch so that the

pouches are still joined in end to end relationship but with a line of weakness which can readily be ruptured.

Somewhat similar equipment can also be used for creating pouches containing other products, such as sugar or sauces (for use in restaurants).

According to the present invention, there is provided a method of forming a transdermal patch, which comprises the steps of:

feeding at a first linear speed a strip of materials comprising a disposable layer, a layer of adhesive and a layer of a permeable membrane;

feeding into close proximity and in face-to-face relationship with the first strip at least one second strip formed of impermeable backing material(s), at the same first linear speed;

passing the first and second strips together through a first sealing station at which at least the opposed longitudinal edge regions of the strips are secured together, optionally with intermediate regions of the strips being secured along their lengths, so as to form at least one elongate chamber;

passing the first and second strips joined at least at their longitudinal edges, through a second sealing station at which the strips are sealed to each other transversely at intervals along the strips, whereby the or each chamber becomes an open-topped pouch;

introducing a liquid containing an active substance into the pouch or pouches, once formed; and

sealing the pouches along their previously open edges so as to form completely sealed pouches.

The process is continuous as a result of the dosing and patch formation happening in a synchronised/simultaneous manner. This is distinct from

the blister technique which is a station-by-station function and non-continuous.

Conveniently, at the second sealing station the upper previously open region of a pouch or pouches is sealed and the sealing simultaneously closes the bottom of the pouch or pouches immediately above the first mentioned pouch or pouches.

The method can also include a separation cutting step, in which a transverse cutting exercise takes place so as to separate one sealed pouch containing the active substance from the adjacent pouches upstream and downstream.

If a tear-tab at one corner of the patch is required, a suitable "kiss-cut" function can be provided at this stage. In addition, other functions such as registration, embossing and de-bossing, can be performed at, or immediately after, this stage.

In addition, when the two strips are first brought together and sealed along their longitudinal edges and when there is one or more additional longitudinal seal being created intermediate the edge region seals, then there will be two or more pouches being created, and it is desirable to separate those laterally adjacent pouches at a suitable downstream station. This can be achieved by, for example, rollers acting on opposite sides of the joined strips with at least one of the rollers having a cutting edge so as to separate laterally adjacent pouches.

Preferably, when effecting the method of the present invention, a gas flushing system is employed, which can be achieved by placing a small bore tube adjacent the liquid (gel) delivery tube, which ensures that the pouch will, when sealed, effectively only contain the gel itself and the flushing gas, for example nitrogen. Alternatively, instead of employing an inert flushing gas, the filling and sealing can be

effected in a "vacuum".

The sealing of the adjacent strips can be effected by opposing pairs of sealing devices (e.g. heated rollers), and the means by which the liquid (gel) containing the active substance is introduced can take the form of a tube the lower, open end of which can be at a level considerably below the axes of rotation of those sealing devices, and can be positioned at a level just above where the transverse sealers are employed which come together intermittently to provide the transverse seals across the strips at the desired spaced intervals. It will be appreciated that careful synchronisation of the different pieces of equipment which carry out the sealing and cutting steps is required, but existing technology is readily available for this.

When it is desired to increase the active amount of substance, whilst retaining the concentration of the active substance constant in the gel, it is clearly necessary to provide a larger volume of the gel. In order to accommodate the larger volume, the pouch needs to be larger and this can be achieved in one or more ways. If, for instance, during pouch production three pouches are being produced side by side, it is possible to reduce the number of pouches to two which will increase the available width of each pouch. This is done by removing one of the pairs of sealing devices (e.g. heating rollers) and adjusting the location of the remaining intermediate pair of sealing devices; moreover, one of the dosing nozzles is removed.

Alternatively, or in addition, the timing of the transverse sealing is adjusted to take place at longer intervals with the result that longer pouches are formed.

Obviously, when the transverse sealing is less frequent during the formation of the longer pouches, it

is also necessary that there is corresponding adjustment to the transverse cutting equipment so that the cutting remains along the seal which separates one sealed pouch or row of pouches from the adjacent pouch or row of pouches.

It is to be appreciated that, even when the volume of the pouch is being altered, it is possible to continue to feed in the first and second strips at the same linear feed speed. In fact, this is a great advantage of the present invention in that variation in the volume of the pouch desired does not necessitate any alteration to the components responsible for feeding in the two starting strips of material. The handling of such strips is a delicate matter and it is therefore of considerable advantage to maintain the feed speeds at a constant. It is a relatively simple matter, through the appropriate control equipment, to cause the transverse sealing components to operate at longer or shorter intervals so as to produce longer or shorter pouches, and equally it is relatively simple for the same control equipment to coordinate the components responsible for the transverse cutting without re-tooling the machine.

The tube or tubes, or like, responsible for injecting the gel containing the active substance into the pouches remains in the same position and injects the appropriate volume of gel into the pouch as the transverse seal is being formed or immediately after it has been formed. Accurate dosing equipment is available to ensure that precisely the desired amount of gel is deposited into each pouch and can be adjusted to compensate for an increase, or decrease, in the volumetric requirements of the pouch in a similar way to the timing adjustment of the sealing devices.

For a better understanding of the present invention, and to show how the same may be carried into

effect, reference will now be made, by way of example, to the accompanying drawing, which shows a perspective view of a method in accordance with the present invention being conducted on equipment having the appropriate facilities to effect the method.

In the drawing there are shown a roll 1 of backing material in the form of a strip 2 which is drawn off from the roll 1 and passed around a tensioning roller 3, then over a guide roller 4 and another guide roller 5 and passed further downstream. Somewhat similarly, but starting from the opposite side of the equipment, there is a roll 6 of multi-layer material (of the type mentioned above) with the strip 7 of that material (e.g. in the form of a laminate) being drawn off from the roll 6 and passed around its own tensioning roller 8 and then around three guide rollers 9, 10 and 11 and downstream into the region of a "nip" 12 where it meets the strip 2. The two strips 2 and 7 pass between three pairs of sealing devices in the form of pairs of heated rollers 13, 14 and 15 which have the effect of sealing the strips 2 and 7 at their longitudinally opposing edge regions 16 and 17 and also at a central location 18, so that the region between the two strips 2 and 7 is divided into two pouches 19 and 20 which are open at their upper and lower ends. However, as those pouches 19 and 20 travel downwardly they encounter the transverse intermittent sealing system which comprises two heated bars 21 and 22 which are generally separated from each other but intermittently are brought together to form a horizontal seal across the downwardly travelling strips 2 and 7 whereby the pouches 19 and 20 are then sealed along their lower edges, as well as their vertical edges. Not shown (for the sake of clarity) are two tubes which project into the pouches 19 and 20 with the lower end regions of the tubes being just above the heated bars 21 and 22. Adjacent those

two tubes are two smaller tubes (also not shown) through which an inert gas (particularly nitrogen) under pressure is introduced into the pouches 19 and 20 to create an inert atmosphere during the dosing of the pouches by the introduction of discrete doses of gel through the main tubes into the pouches 19 and 20. When the heated bars 21 and 22 are separated the filled pouches 19 and 20 can move further downward to the position occupied by the pouches 23 and 24. It can readily be seen that the heating and sealing action of the bars 21 and 22 simultaneously seals the lower edges of the pouches 19 and 20 and the upper edges of the pouches 23 and 24. It is also to be appreciated that the strips 2 and 7 when separate and when travelling together move at the same linear speed throughout in a continuous manner. For this reason the bars 21 and 22, when acting on the strips 2 and 7, move at the same speed as those strips so that the smooth progress of those strips is not impaired.

Shown below the pouches 23 and 24 are two further pouches 25 and 26 produced immediately before the production of the pouches 23 and 24. As shown in the drawing, the lower edge of the pouches 25 and 26 is being acted on by cutting devices 27 and 28 which cut transversely across the combined strips 2 and 7 to separate the pair of pouches 25 and 26 from the pair 29 shown below as pouches 30 and 31.

It can readily be appreciated that comprehensive equipment, such as a bandolier mechanism, can be employed to draw off the strips 2 and 7 at a uniform speed and to feed them into the sealing system consisting of the heated rollers 13, 14 and 15 at the same speed and to pass the united strips 2 and 7 through the sealing system 21, 22 and through the cutting system 27, 28 at the same uniform speed.

If longer pouches are required, it is merely

necessary to cause the sealing system 21, 22 to operate for the same duration but at greater intervals and for the cutting system 27, 28 also to operate at correspondingly greater intervals. It will also readily be appreciated that the provision of the three pairs 13, 14 and 15 of heated rollers of the sealing system causes the production of two pouches 19 and 20, and that by increasing or decreasing the number of pairs of heated rollers or other sealing devices there is a corresponding increase or decrease in the number of pouches generated in side-by-side relationship.

The dosing through the tubes (not shown) of the gel containing the active substance (e.g. nicotine) can be effected by sophisticated dosing equipment which is available on the market, for example from the company Hibar Systems Limited.

Although the dosing of the gel through the tube or tubes into the pouch or pouches is effected as intermittent deposits, the supply of the inert gas through the adjacent tube or tubes to create an inert atmosphere in the pouch or pouches being formed can be effected continuously.

With suitable control equipment it will be possible, at the touch of a button, to alter the location of the heated rollers 13, 14 and 15 thereby varying the width of the pouches and also to alter the frequency of the sealing operation of the heating components 21, 22 and cutting components 27, 28 so as to vary the length of the pouches. No re-tooling is necessary. Thus variation in the magnitude of the pouches can be effected without having to replace any of the components of the equipment by replacement components. All that needs to be varied is the location of the heated rollers 13, 14 and 15 and/or the frequency of operation of the transverse sealing system, 21, 22 and the cutting system 27, 28. If

desired, the backing material can be flesh-coloured or clear on that side which is to face outwards when the patch is applied to a person. At further stages downstream, the individual pouches can be cropped to provide a 'kiss-cut' 'tear-tab' and be separately packed in their own individual wrappers and batches of the wrappers collected together in packets or other suitable containers.

PCT/GB 99/01138

Hapeltine Lake.

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